PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X-16040	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US 03/32746	International filing date *(day/month/year)* 10.11.2003	Priority date *(day/month/year)* 22.11.2002
International Patent Classification (IPC) or both national classification and IPC C07D487/04		
Applicant ELI LILLY AND COMPANY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 13 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28.04.2004	16.12.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Frelon, D Telephone No. +49 30 25901-312

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/32746

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-39 as originally filed

Claims, Numbers

1-5 filed with telefax on 10.11.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-5
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item I

Within the Applicant's letter of 10.11.2004 received by fax on the same day, amendments have been filed and commented as following:

1. Claim 1 (Formula 1)

The misplaced "ethylene" has been deleted from the definitions of R_1 and R_2. The unclear "phenanthrolene" has been deleted from the definition of R_2.

The definition of Q_1 has been amended on the basis of previous claim 3. This definition remains unfortunately unclear: It appears like an alternative where Q_1 would have two possible definitions:
- a first one: "when m and n are independently 0-2, except when one is 0 the other cannot be 0" and
- a second one: "when m and n are independently 0-2, but one or the other of m or n is not 0".

In fact, these wordings, which appear different, may actually have the same meaning. There is no real alternative in the present definition of Q_1 and such an unclarity has not been corrected. In comparison, a similar alternative stressed for Q_2 is clear.

[*Note additionally the inconsistent punctuation: in the first case, there is no punctuation between pyridyl and when... etc, and in the second case, a semi-colon is between N-benzimidazolino and when... etc. It is therefore even not clear, in the first case, whether the sentence part "when...etc" applies only to pyridyl or to the whole first case definition of Q_1 as it can be interpreted for the second case definition of Q_1*]

The possibilities for R_{11} and R_{10} or R_{11} and R_{12} or R_{21} and R_{20} or R_{24} and R_{25} or R_{32} and R_{33} or R_{41} and R_{40} to form together a (hetero)ring have been deleted.

Unconsistencies about Q_3 (as a bond or taken with R_{35}) have been deleted.

2. Claim 2 (Formula 1)

The same deletions of "ethylene" have been made as in claim 1.
The same remark concerning Q_1 should be made as for claim 1.

Same deletions of the possible (hetero)rings formations have been made as for claim 1. Unconsistencies about Q_3 have been deleted like in claim 1.

[*Note the unnecessary and obscuring repetition of the same definitions which could have been avoided by an appropriate reference to the previous claim*]

3. Claim 3 (Formula II)

The same deletions of "ethylene" have been made as in claim 1 and, additionally, in the definitions of R6' and R_7.

Maintained as originally filed, Q_1 remains ambiguously drafted: the corresponding remark made above should be repeated as for claims 1 and 2.

Same deletions of the possible (hetero)rings formations have been made as in claims 1 and 2. Q_3 has been corrected as in claims 1 and 2.

[*Note the dependency of claim 3 on claim 2 is erroneous if one considers that the definitions of the substituents of R_1 wherein, in claim 2, one can read a correctly specified "C_1-C_4)dialkylaminomethyl" and not in claim 3 which reads "dialkylaminomethyl"; the same remark applies about the definitions of R_{11} and R_{12} which correctly read "(C_3-C_8)cycloalkyl" and "(C_3-C_8)cycloalkylmethyl" and claim 2 and not in claim 3 which reads "cycloalkyl" and "cycloalkylmethyl"*] (see following point 5).

4. Claim 4 (Formula III) and claim 5 (all examples 1-4)

Claims 4 and 5 repeat originally filed claims 4 and 5.

5. The arylalkyl, aryl groups have not been specified as required where relevant, esp. in the definitions of R_1, R_2, R_{11}, R_{12}, R_{16}, R_{22}. The same remark applies to the unspecified "N,N'-dialkylcarbamoyloxy" in R_2, R6' and R_7.

Re Item V

1. Cited documents

D1: WO 02/062787
D2: WO 02/062794
D3: WO 02/066462
D4: WO 01/16138
D5: WO 02/094833 intermediate document, cited in the application
D6: WO 2004/013135 intermediate document
D7: WO 2004/026871 intermediate document

The intermediate documents D5-D7 are relevant for the purposes of Rules 33.1 c, 64.3 and 70.10 PCT, but since the priority documents are not available at the time of establishing the written opinion, they are not taken into account. It is based on the assumption that all claims enjoy priority rights from the filing date of the priority document(s). If it later turns out that this assumption is not correct, the intermediate documents in the International Search Report (ISR) could become relevant in order to assess whether the claims satisfy the criteria set forth in Article 33(1) PCT.
If the priority date is not valid for the complete claimed subject-matter, these documents may become relevant prior art in a possible regional/national phase.

2. Novelty

In view of the prior art, the present invention differs essentially by the condensation on the pyrazol core with a 7-membered carbocyclic ring optionally substituted by one or more C_1-C_6-alkyl group. In D1 to D3, there is no such condensation on the pyrazole. In D4 the condensed ring includes a heteroatom and a phenyl is in place of the pyridine on the 3-position of the pyrazole. Substitution patterns corresponding to R_1 and R_2 are comparable.

3. Inventive step

3.1 According to the description (pages 1 and following), the problem underlying the present application is to provide pyrazoloazepine derivatives which are TGF-beta signal transduction inhibitors and, as such, useful for example in the treatment of cancers, fibrosis, angiogenesis, nephropathies, autoimmune disorders, HIV, Alzheimer's disease and/or atherosclerosis (pages 33-38).

3.2 Compounds of the closest prior art seen in D1-D3 are disclosed for the same properties. All compounds have in common the 3-pyridinyl, 4-(hetero)(bi)aryl-pyrazole group. No mention or indication of a possible further condensation on the pyrazole can be found by the skilled person in the state of the art, except in D4 wherein the condensed structure should include a heteroatom for compounds which are also said to be useful against inflammation, arthritis and cancers.

It is noted that, from the point of view of the biological impact which is sought (prophylaxy, therapy), different modes of action (as site interactions) may be involved which achieve a same final effect (or application). Modes of action of compounds may stay unknown for a while and once, thanks to the continuous advance of the technology, a mechanism will be intimately elucidated (here a TGF-beta signal transduction inhibition). Such an inherent property of compounds is a mere discovery and thus not patentable as such. It is also never excluded, unless prove of the contrary is given, that a same molecule may interact on different active sites.

For instance, in the present case, compounds of D4 which possess common basic structural elements are known to be COX-2 inhibitors with common therapeutical aims. To some extent, the non-condensed form might have been considered as a structure necessary for the activity but, by introduction of a further condensation which does not dramatically affect this core (see, for instance, the examples in which R_3 is always H), the skilled person expects to maintain certain activities, especially the ones common to D4.

However, if an unexpected property or use could be put in application with the claimed compounds, this would indicate that an invention has actually been made and, under the reservation that no other objection is maintained, may be patentable. At present, no data nor test results has been disclosed showing that the claimed compounds, specifically condensed with a 7-membered saturated carbocyclic ring, are actually active compounds in order to substantiate the presence of an inventive step as required by the PCT. The problem to provide further compounds as claimed appears therefore obviously solved.

3.3 The Applicant's attention is drawn to the fact that the claims as presently drafted do not fully satisfy PCT requirements. Particularly, the protection which is sought should comply with a reasonable breadth of a scope covering only variants/compounds which solve the problem underlying the invention.

It is realized that the Applicant is entitled to claim all obvious modifications of what was concretely described, *i.e.* a certain number of examples, and that alternative variations have to be supported by the description.

Claims as drafted, especially claim 1, (including open expressions/terms like "*alkyl, arylalkyl, aryl, etc*", derivatives thereof used without further definitive qualifications) cover a very large amount of variations and combinations and, therefore, extend the scope of the claims beyond what has actually been investigated by the inventor(s). Such a generalisation (breadth of the scope) appears ***speculative*** in view of the closeness of the prior art and of the given illustration which is relatively limited since presently all prepared compounds correspond to structures wherein: R_1 is H; R_2 is a quinolin-4-yl; and R_3 is H.

It can be therefore questioned whether all forms covered by the large claimed scope are actually part of the invention, depending on which criterion the acknowledgment of an inventive step should based. It can also be questioned whether the constant features found in the illustrative examples form a necessary characterisitic of the invention which should not vary out of the ***reasonable*** extent of the usual equivalents and (bio)isosters.

The extent of a "reasonable generalisation" also depends on the extent of the illustration and also upon the relative distance to the prior art compounds which presently is very close.

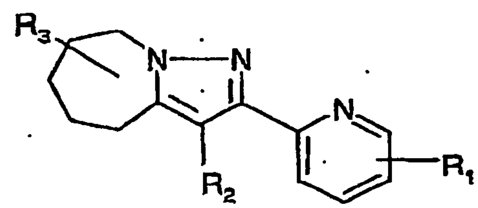
There is indeed a great variety of structural possibilities which are claimed and not yet explored by the Applicant, the *effect of which cannot be foreseen* having regard to the problem underlying the present application and consequently which are not solutions of the problem. The meanings of the substituents are also to be considered in view of the reproducibility and the feasablity of the invention in all its claimed aspects. Thus it cannot be ascertained that all the encompassed compounds fall within the scope of the claims of the present application and/or constitute actual solutions to the problem underlying the application.

In conclusion, the inventive step required by Article 33 (3) PCT can be acknowledged only for a well-defined scope embracing a reasonable generalisation of the very invention as illustrated. It should have been credible that the unexpected effect on which the

acknowledgment of an inventive step should have been based concerns also all the claimed compounds.

WE CLAIM:

1. A compound according to the structure



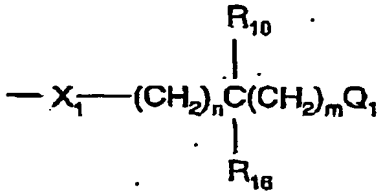
Formula 1

wherein R_1 may be one or more optional substituents selected from the group consisting of: (C1-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C1-C6)alkoxy, (C2-C6)alkenyloxy, (C2-C6)alkynyloxy, (C1-C6)alkylthio, (C1-C6)alkylsulphinyl, (C1-C6)alkylsulphonyl, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, (C1-C6)alkoxycarbonyl, N-(C1-C6)alkylcarbamoyl, N,N-di-[(C1-C6)alkyl]carbamoyl, (C2-C6)alkanoyl, (C2-C6)alkanoyloxy, (C2-C6)alkanoylamino, N-(C1-C6)alkyl-(C2-C6)alkanoylamino, (C3-C6)alkenoylamino, N-(C1-C6)alkyl-(C3-C6)alkenoylamino, (C3-C6)alkynoylamino, N-(C1-C6)alkyl-(C3-C6)alkynoylamino, N-(C1-C6)alkylsulphamoyl, N,N-di-[(C1-C6)alkyl]sulphamoyl, (C1-C6)alkanesulphonylamino, N-(C1-C6)alkyl-(C1-C6)alkanesulphonylamino, carboxamide, thiophenyl, aminophenyl, trifluoromethyl, halo, trifluoromethoxy, hydroxymethyl, N-pyrrolidino, N-morpholino, phenylthio, (C1-C4)dialkylaminomethyl, methoxyphenyl, amino, hydroxy, carboxyl, phenyl, arylalkyl;

R_2 is unsubstituted or substituted quinoline; unsubstituted or substituted quinoline N-oxide; unsubstituted or substituted phenyl; unsubstituted or substituted naphthalene; unsubstituted or substituted pyridine; unsubstituted or substituted pyridine N-oxide; unsubstituted or substituted quinazoline; unsubstituted or substituted cinnoline; unsubstituted or substituted benzodioxole; unsubstituted or substituted benzodioxane; unsubstituted or substituted pyrimidine; unsubstituted or substituted benzothiophene; wherein the substitution may independently be one or more of the following: (C1-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C1-C6) alkylhalide, (C1-C6)alkoxy, (C2-C6)alkenyloxy, (C2-C6)alkynyloxy, (C1-C6)alkylthio, (C1-C6)alkylsulphinyl, (C1-

C6)alkylsulphonyl, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, (C1-C6)alkoxycarbonyl, N-(C1-C6)alkylcarbamoyl, N,N-di-[(C1-C6)alkyl]carbamoyl, aminooxy, N-(C1-C6)alkyl aminooxy , N,N-di-[(C1-C6)alkyl]aminooxy, (C2-C6)alkanoyl, (C2-C6)alkanoyloxy, (C2-C6)alkanoylamino, N-(C1-C6)alkyl-(C2-C6)alkanoylamino, (C3-C6)alkenoylamino, N-(C1-C6)alkyl-(C3-C6)alkenoylamino, (C3-C6)alkynoylamino, N-(C1-C6)alkyl-(C3-C6)alkynoylamino, sulphamoyl, N-(C1-C6)alkylsulphamoyl, N,N-di-[(C1-C6)alkyl]sulphamoyl, (C1-C6)alkanesulphonylamino, N-(C1-C6)alkyl-(C1-C6)alkanesulphonylamino, carboxamide, phenyl, thiophenyl, aminophenyl, phenylthio, halo, cyano, pyridinyl, arylalkyl, hydroxy, N-pyrrolidino, N-morpholino, carboxyl, [5-phenyl-1,2,4-oxadiazole-3-yl]methoxy, 6-methyl-pyridazin-3-yloxy, (5-oxo-2-pyrrolidinyl)methoxy, 2-(4,5-dihydro-1H-imidazolyl), N, N-dialkylcarbamoyloxy, 1-hydroxy-1-methylethyl, 4-fluorophenyl, 3,4-methylenedioxyphenyl, trifluoromethyl, trifluoromethoxy,

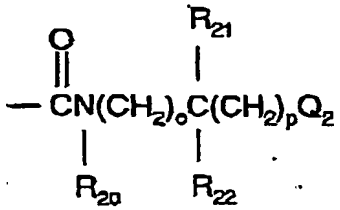
or a group of the formula:



wherein: X_1 is O, N, S, SO_2, NR_{13}, C(O), or bond; Q_1 is hydrogen, phenyl, 5-(2,2-difluoro-1,3-benzodioxolyl), $C(O)Q_5$, or pyridyl when m and n are independently 0-2, except when one is 0 the other cannot be 0; Q_1 is OR_{11}, $NR_{11}R_{12}$, halo, N-morpholino, N-piperazino-N'R_{13}, N-imidazolyl, N-pyrazolyl, N-triazolyl, N-(4-piperidinylpiperidine), SO_2R_{14}, SOR_{14}, $NHSO_2R_{15}$, acetamido, N-phthalimido, N-oxazolidino, N-imidazolino, N-benzoxazolidino, N-pyrolidinonyl, N(N'-methylbenzimidazolino), N,N-di(C1-C4)alkylamino(C1-C4)alkoxy, N-benzimidazolino; when m and n are independently 0-2, but one or the other of m or n is not 0; Q_5 is hydroxy, methoxy, amino, diethylamino, dimethylamino; R_{10} is hydrogen, halo, (C1-C6)alkyl; R_{11} and R_{12} are independently hydrogen, (C1-C6)alkyl, (C1-C6)alkoxy, arylalkyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkylmethyl, 4-(N-methylpiperidinyl), or pyridyl; R_{13} is hydrogen, (C1-C6)alkyl, 2-methoxyphenyl, 2-pyridimidinyl; R_{14} is 2-pyrimidinyl, N-methyl-2-imidazolyl, 4-

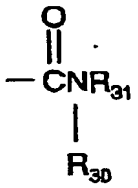
chlorophenyl, 2-pyridylmethyl; R_{15} is (C1-C6)alkyl, N-methyl-4-imidazolyl; R_{16} is hydrogen, halo, arylalkyl, aryl,

or a group of the formula:



wherein: Q_2 is hydrogen, 4-imidazolyl, or $C(O)NR_{24}R_{25}$ when o and p are independently 0-2; Q_2 is OR_{23}, $NR_{24}R_{25}$, or N-morpholino, when o and p are independently 0-2, but one or the other of o or p is not 0; R_{20} is hydrogen, or (C1-C6)alkyl; R_{21} is hydrogen or (C1-C6)alkyl; R_{22} is hydrogen, (C1-C6)alkyl, arylalkyl, or aryl; R_{23} is hydrogen or (C1-C6)alkyl; R_{24} is hydrogen or (C1-C6)alkyl; R_{25} is hydrogen, (C1-C6)alkyl, or acetyl,

or a group of the formula:

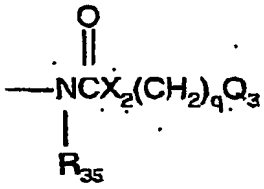


wherein: R_{30} is hydrogen, or (C1-C6)alkyl; R_{31} is hydrogen, (C1-C6)alkyl, 2-pyridyl, pyridylmethyl, amino, or hydroxy,

or a group of the formula:

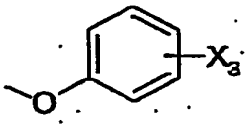
wherein: R_{32} and R_{33} are each independently hydrogen, (C1-C6)alkyl, acetyl or (C1-C4)alkylsulphonyl,

or a group of the formula:



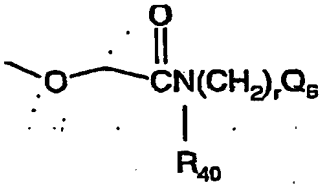
wherein: X_2 is CH_2, O, or N; q is 0-3; Q_3 is $NR_{36}R_{37}$, or OR_{38}, and R_{35} is hydrogen; R_{36}, R_{37}, and R_{38} are each independently hydrogen, or (C1-C6)alkyl,

or a group of the formula:



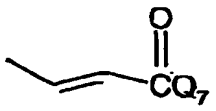
wherein: X_3 is cyano, carboxamide, N,N-dimethylcarboxamide, N,N-dimethylthiocarboxamide, N,N-dimethylaminomethyl, 4-methylpiperazin-1yl-methyl or carboxylate,

or a group of the formula:



wherein: Q_6 is $NR_{41}R_{42}$; r is 2-3; R_{40} is hydrogen, or (C1-C6)alkyl; R_{41} and R_{42} are hydrogen or (C1-C6)alkyl,

or a group of the formula:

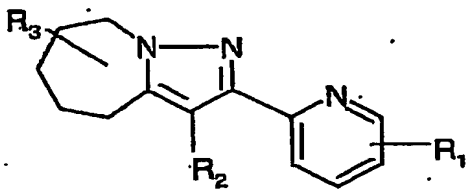


wherein: Q_7 is hydroxy, methoxy, dimethylamino, or N-piperidinyl;

R_3 may be one or more optional substituents selected from the group consisting of (C1-C6 alkyl);

and the pharmaceutically acceptable salts thereof.

2. A compound according to the structure:



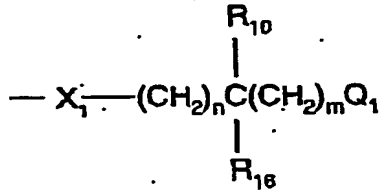
Formula 1

wherein R_1 may be one or more optional substituents selected from the group consisting of: (C1-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C1-C6)alkoxy, (C2-C6)alkenyloxy, (C2-C6)alkynyloxy, (C1-C6)alkylthio, (C1-C6)alkylsulphinyl, (C1-C6)alkylsulphonyl, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, (C1-C6)alkoxycarbonyl, N-(C1-C6)alkylcarbamoyl, N,N-di-[(C1-C6)alkyl]carbamoyl, (C2-C6)alkanoyl, (C2-C6)alkanoyloxy, (C2-C6)alkanoylamino, N-(C1-C6)alkyl-(C2-C6)alkanoylamino, (C3-C6)alkenoylamino, N-(C1-C6)alkyl-(C3-C6)alkenoylamino, (C3-C6)alkynoylamino, N-(C1-C6)alkyl-(C3-C6)alkynoylamino, N-(C1-C6)alkylsulphamoyl, N,N-di-[(C1-C6)alkyl]sulphamoyl, (C1-C6)alkanesulphonylamino, N-(C1-C6)alkyl-(C1-C6)alkanesulphonylamino, carboxamide, thiophenyl, aminophenyl, trifluoromethyl, halo, trifluoromethoxy, hydroxymethyl, N-pyrrolidino, N-morpholino, phenylthio, (C1-C4)dialkylaminomethyl, methoxyphenyl, amino, hydroxy, carboxyl, phenyl, arylalkyl;

R_2 is substituted or unsubstituted quinoline; substituted or unsubstituted quinoline N-oxide;

wherein the substitution may independently be one or more of the following: (C1-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C1-C6) alkylhalide, (C1-C6)alkoxy, (C2-C6)alkenyloxy, (C2-C6)alkynyloxy, (C1-C6)alkylthio, (C1-C6)alkylsulphinyl, (C1-C6)alkylsulphonyl, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, (C1-C6)alkoxycarbonyl, N-(C1-C6)alkylcarbamoyl, N,N-di-[(C1-C6)alkyl]carbamoyl, aminooxy, N-(C1-C6)alkyl aminooxy , N,N-di-[(C1-C6)alkyl]aminooxy, (C2-C6)alkanoyl, (C2-C6)alkanoyloxy, (C2-C6)alkanoylamino, N-(C1-C6)alkyl-(C2-C6)alkanoylamino, (C3-C6)alkenoylamino, N-(C1-C6)alkyl-(C3-C6)alkenoylamino, (C3-C6)alkynoylamino, N-(C1-C6)alkyl-(C3-C6)alkynoylamino, sulphamoyl, N-(C1-C6)alkylsulphamoyl, N,N-di-[(C1-C6)alkyl]sulphamoyl, (C1-C6)alkanesulphonylamino, N-(C1-C6)alkyl-(C1-C6)alkanesulphonylamino, carboxamide, phenyl, thiophenyl, aminophenyl, phenylthio, halo, cyano, pyridinyl, arylalkyl, hydroxy, N-pyrrolidino, N-morpholino, carboxyl, [5-phenyl-1,2,4-oxadiazole-3-yl]methoxy, 6-methyl-pyridazin-3-yloxy, (5-oxo-2-pyrrolidinyl)methoxy, 2-(4,5-dihydro-1H-imidazolyl), N, N-dialkylcarbamoyloxy, 1-hydroxy-1-methylethyl, 4-fluorophenyl, 3,4-methylenedioxyphenyl, trifluoromethyl, trifluoromethoxy,

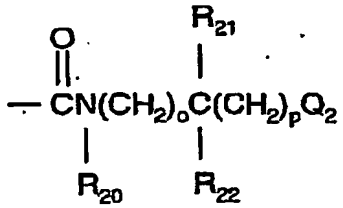
or a group of the formula :



wherein: X_1 is O, N, S, SO_2, NR_{13}, C(O), or bond; Q_1 is hydrogen, phenyl, 5-(2,2-difluoro-1,3-benzodioxolyl), $C(O)Q_5$, or pyridyl when m and n are independently 0-2, except when one is 0 the other cannot be 0; Q_1 is OR_{11}, $NR_{11}R_{12}$, halo, N-morpholino, N-piperazino-N'R_{13}, N-imidazolyl, N-pyrazolyl, N-triazolyl, N-(4-piperidinylpiperidine), SO_2R_{14}, SOR_{14}, $NHSO_2R_{15}$, acetamido, N-phthalimido, N-oxazolidino, N-imidazolino, N-benzoxazolidino, N-pyrolidinonyl, N(N'-methylbenzimidazolino), N,N-di(C1-C4)alkylamino(C1-C4)alkoxy, N-benzimidazolino; when m and n are independently 0-2, but one or the other of m or n is not 0; Q_5 is hydroxy, methoxy, amino, diethylamino, dimethylamino; R_{10} is hydrogen, halo, (C1-C6)alkyl; R_{11} and R_{12} are independently

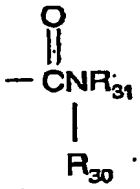
hydrogen, (C1-C6)alkyl, (C1-C6)alkoxy, arylalkyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkylmethyl, 4-(N-methylpiperidinyl) or pyridyl; R_{13} is hydrogen, (C1-C6)alkyl, 2-methoxyphenyl, 2-pyridimidinyl; R_{14} is 2-pyrimidinyl, N-methyl-2-imidazolyl, 4-chlorophenyl, 2-pyridylmethyl; R_{15} is (C1-C6)alkyl, N-methyl-4-imidazolyl; R_{16} is hydrogen, halo, arylalkyl, aryl,

or a group of the formula:



wherein: Q_2 is hydrogen, 4-imidazolyl, or $C(O)NR_{24}R_{25}$ when o and p are independently 0-2; Q_2 is OR_{23}, $NR_{24}R_{25}$, or N-morpholino, when o and p are independently 0-2, but one or the other of o or p is not 0; R_{20} is hydrogen, or (C1-C6)alkyl; R_{21} is hydrogen or (C1-C6)alkyl; R_{22} is hydrogen, (C1-C6)alkyl, arylalkyl or aryl; R_{23} is hydrogen or (C1-C6)alkyl; R_{24} is hydrogen or (C1-C6)alkyl; R_{25} is hydrogen, (C1-C6)alkyl, or acetyl,

or a group of the formula:

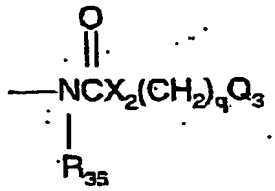


wherein: R_{30} is hydrogen, or (C1-C6)alkyl; R_{31} is hydrogen, (C1-C6)alkyl, 2-pyridyl, pyridylmethyl, amino, or hydroxy,

or a group of the formula:

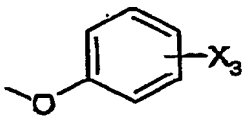
wherein: R_{32} and R_{33} are each independently hydrogen, (C1-C6)alkyl, acetyl or (C1-C4)alkylsulphonyl,

or a group of the formula:



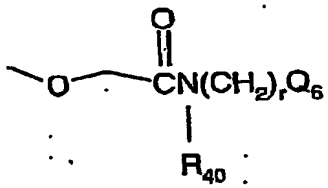
wherein: X_2 is CH_2, O, or N; q is 0-3; Q_3 is $NR_{36}R_{37}$, or OR_{38}, and R_{35} is hydrogen; R_{36}, R_{37}, and R_{38} are each independently hydrogen, or (C1-C6)alkyl,

or a group of the formula:



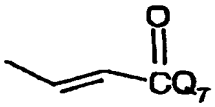
wherein: X_3 is cyano, carboxamide, N,N-dimethylcarboxamide, N,N-dimethylthiocarboxamide, N,N-dimethylaminomethyl, 4-methylpiperazin-1yl-methyl or carboxylate,

or a group of the formula:



wherein: Q_6 is $NR_{41}R_{42}$; r is 2-3; R_{40} is hydrogen, or (C1-C6)alkyl; R_{41} and R_{42} are hydrogen or (C1-C6)alkyl,

or a group of the formula:

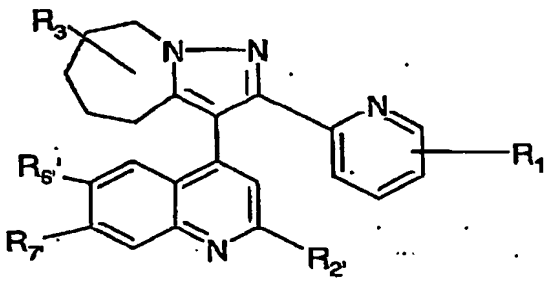


wherein: Q_7 is hydroxy, methoxy, dimethylamino, or N-piperidinyl;

R_3 may be one or more optional substituents selected from the group consisting of (C1-C6 alkyl);

and the pharmaceutically acceptable salts thereof.

3. A compound according to claim 2 of the formula:



Formula II

wherein R_1 may be one or more optional substituents selected from the group consisting of: (C1-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C1-C6)alkoxy, (C2-C6)alkenyloxy, (C2-C6)alkynyloxy, (C1-C6)alkylthio, (C1-C6)alkylsulphinyl, (C1-C6)alkylsulphonyl, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, (C1-C6)alkoxycarbonyl, N-(C1-C6)alkylcarbamoyl, N,N-di-[(C1-C6)alkyl]carbamoyl, (C2-C6)alkanoyl, (C2-C6)alkanoyloxy, (C2-C6)alkanoylamino, N-(C1-C6)alkyl-(C2-C6)alkanoylamino, (C3-C6)alkenoylamino, N-(C1-C6)alkyl-(C3-C6)alkenoylamino, (C3-C6)alkynoylamino, N-(C1-C6)alkyl-(C3-C6)alkynoylamino, N-(C1-C6)alkylsulphamoyl, N,N-di-[(C1-C6)alkyl]sulphamoyl, (C1-C6)alkanesulphonylamino, N-(C1-C6)alkyl-(C1-C6)alkanesulphonylamino, carboxamide, thiophenyl, aminophenyl, trifluoromethyl, halo, trifluoromethoxy, hydroxymethyl, N-pyrrolidino, N-morpholino, phenylthio, dialkylaminomethyl, methoxyphenyl, amino, hydroxy, carboxyl, phenyl, arylalkyl;

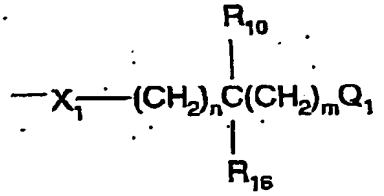
R_3 may be one or more optional substituents selected from the group consisting of (C1-C6 alkyl);

$R_{2'}$ is hydrogen; (C1-C6)alkyl; (C1-C6)alkylthio; (C1-C6)alkoxy; halo; thiophenyl; aminophenyl; N-pyrrolidino; N-morpholino;

R6' and $R_{7'}$ are independently one or more of the following: hydrogen, (C1-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C1-C6) alkylhalide, (C1-C6)alkoxy, (C2-C6)alkenyloxy, (C2-C6)alkynyloxy, (C1-C6)alkylthio, (C1-C6)alkylsulphinyl, (C1-C6)alkylsulphonyl, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino; (C1-

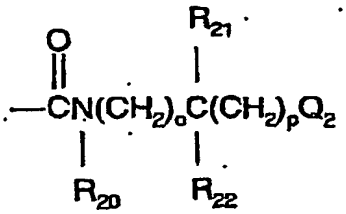
C6)alkoxycarbonyl, N-(C1-C6)alkylcarbamoyl, N,N-di-[(C1-C6)alkyl]carbamoyl, aminooxy, N-(C1-C6)alkyl aminooxy , N,N-di-[(C1-C6)alkyl]aminooxy, (C2-C6)alkanoyl, (C2-C6)alkanoyloxy, (C2-C6)alkanoylamino, N-(C1-C6)alkyl-(C2-C6)alkanoylamino, (C3-C6)alkenoylamino, N-(C1-C6)alkyl-(C3-C6)alkenoylamino, (C3-C6)alkynoylamino, N-(C1-C6)alkyl-(C3-C6)alkynoylamino, sulphamoyl, N-(C1-C6)alkylsulphamoyl, N,N-di-[(C1-C6)alkyl]sulphamoyl, (C1-C6)alkanesulphonylamino, N-(C1-C6)alkyl-(C1-C6)alkanesulphonylamino, carboxamide, phenyl, thiophenyl, aminophenyl, phenylthio, halo, cyano, pyridinyl, arylalkyl, hydroxy, N-pyrrolidino, N-morpholino, carboxyl, [5-phenyl-1,2,4-oxadiazole-3-yl]methoxy, 6-methyl-pyridazin-3-yloxy, (5-oxo-2-pyrrolidinyl)methoxy, 2-(4,5-dihydro-1H-imidazolyl), N, N-dialkylcarbamoyloxy, 1-hydroxy-1-methylethyl, 4-fluorophenyl, 3,4-methylenedioxyphenyl, trifluoromethyl, trifluoromethoxy,

or a group of the formula:



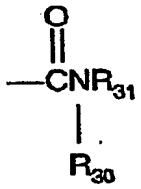
wherein: X_1 is O, N, S, SO_2, NR_{13}, C(O), or bond; Q_1 is hydrogen, phenyl, 5-(2,2-difluoro-1,3-benzodioxolyl), $C(O)Q_5$, or pyridyl when m and n are independently 0-2, except when one is 0 the other cannot be 0; Q_1 is OR_{11}, $NR_{11}R_{12}$, halo, N-morpholino, N-piperazino-N'R_{13}, N-imidazolyl, N-pyrazolyl, N-triazolyl, N-(4-piperidinylpiperidine), SO_2R_{14}, SOR_{14}, $NHSO_2R_{15}$, acetamido, N-phthalimido, N-oxazolidino, N-imidazolino, N-benzoxazolidino, N-pyrolidinonyl, N(N'-methylbenzimidazolino), N,N-di(C1-C4)alkylamino(C1-C4)alkoxy, N-benzimidazolino; when m and n are independently 0-2, but one or the other of m or n is not 0; Q_5 is hydroxy, methoxy, amino, diethylamino, dimethylamino; R_{10} is hydrogen, halo, (C1-C6)alkyl; R_{11} and R_{12} are independently hydrogen, (C1-C6)alkyl, (C1-C6)alkoxy, arylalkyl, cycloalkyl, cycloalkylmethyl, 4-(N-methylpiperidinyl) or pyridyl; R_{13} is hydrogen, (C1-C6)alkyl, 2-methoxyphenyl; R_{14} is 2-pyrimidinyl, N-methyl-2-imidazolyl, 4-chlorophenyl, 2-pyridylmethyl; R_{15} is (C1-C6)alkyl, N-methyl-4-imidazolyl; R_{16} is hydrogen, halo, arylalkyl, aryl,

or a group of the formula:



wherein: Q_2 is hydrogen, 4-imidazolyl, or $C(O)NR_{24}R_{25}$ when o and p are independently 0-2; Q_2 is OR_{23}, $NR_{24}R_{25}$, or N-morpholino, when o and p are independently 0-2, but one or the other of o or p is not 0; R_{20} is hydrogen, or (C1-C6)alkyl; R_{21} is hydrogen or (C1-C6)alkyl; R_{22} is hydrogen, (C1-C6)alkyl, arylalkyl or aryl; R_{23} is hydrogen or (C1-C6)alkyl; R_{24} is hydrogen, (C1-C6)alkyl; R_{25} is hydrogen, (C1-C6)alkyl, or acetyl,

or a group of the formula:

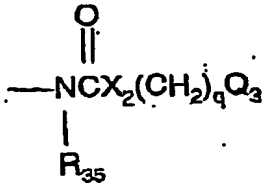


wherein: R_{30} is hydrogen, or (C1-C6)alkyl; R_{31} is hydrogen, (C1-C6)alkyl, 2-pyridyl, pyridylmethyl, amino, or hydroxy;

or a group of the formula:

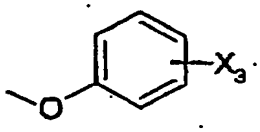
wherein: R_{32} and R_{33} are each independently hydrogen, (C1-C6)alkyl, acetyl or alkylsulphonyl,

or a group of the formula:



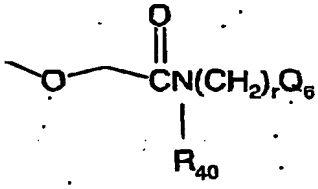
wherein: X_2 is CH_2, O, or N; q is 0-3; Q_3 is $NR_{36}R_{37}$ or OR_{38}; R_{35} is hydrogen; R_{36}, R_{37}, and R_{38} are each independently hydrogen, or (C1-C6)alkyl,

or a group of the formula:



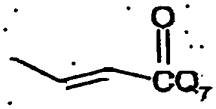
wherein: X_3 is cyano, carboxamide, N,N-dimethylcarboxamide, N,N-dimethylthiocarboxamide, N,N-dimethylaminomethyl, 4-methylpiperazin-1yl-methyl or carboxylate,

or a group of the formula:



wherein: Q_6 is $NR_{41}R_{42}$; r is 2-3; R_{40} is hydrogen, or (C1-C6)alkyl; R_{41} and R_{42} are hydrogen or (C1-C6)alkyl,

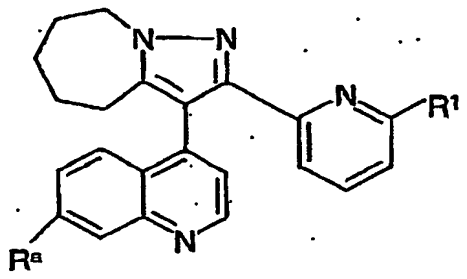
or a group of the formula:



wherein: Q_7 is hydroxy, methoxy, dimethylamino, or N-piperidinyl;

and the pharmaceutically acceptable salts thereof.

4. A compound of the formula:



Formula III

wherein

R^1 is hydrogen or methyl;

R^a is hydroxy; (C1-C4)alkoxy; or $-O(CH_2)_2N$-morpholino;

and the pharmaceutically acceptable salts thereof.

5. A compound according to claim 1 selected from the group consisting of:

a. 3-quinolin-4-yl-2-pyridin-2-yl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a]azepine.

b. (7-Methoxy-quinolin-4-yl)-2-pyridin-2-yl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5a]azepine.

c. 4-(2-Pyridin-2-yl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a]azepin-3-yl)-quinolin-7-ol.

d. 3-[7-(2-Morpholin-4-yl-ethoxy)-quinolin-4-yl]-2-pyridin-2-yl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a]azepine.

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